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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,100	CARR, FRANCIS J	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-74* is/are pending in the application.

4a) Of the above claim(s) *16-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 16-74 are pending in the application.

Claims 16-51 are withdrawn from consideration, as being drawn to non-elected invention.

Claims 1-15 have been cancelled.

Claims 52-74 are under examination.

Specification

The disclosure is objected to because of the informalities as set forth in the Office action of 8/25/2004 and reiterated as follows: There are no Seq. ID Nos. for the peptide sequences at page 3, lines 8 and 9; page 5, lines 1 and 5; page 26, line 7. Applicant should check for other peptide or nucleic acid sequences without any Seq. ID. No. in the specification.

Response to Arguments

Applicant states that a revised sequence listing will be provided in due course to reflect the sequences on pages 3, 5, and 26.

In reply, in the absence of new sequence listing, the objection to the specification has not been overcome.

Withdrawn Rejection

In view of the amendments to the claims the following rejections are withdrawn: the 35 USC 101 and 35 USC 102 over Chen and Georgiou.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, first paragraph

Claims 52-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and reiterated below.

Written Description:

The specification fails to provide an adequate written description of the claimed library that encompasses a huge genus of a protein of no definite sequences/structures. The claimed library of protein that comprises one or more individual identifier sequence amino acid tracts does not recite the kind and/or length of these individual amino acid sequence tracts. Nor does it describe how it is unique from one another and/or its location in the protein sequences. Furthermore, there is no

description as to the kind of protease sensitive sites and/or the protease to which the sites are considered sensitive thereto. The claim recites far too numerous variables for each of the recited variable. A "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials". University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993). See also University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003). The description in the specification drawn to scFv with specific random tract and specific enzyme protease is not a description of the genus claim. Neither does the specification disclose that even for this specific species different types of enzymes can be used. There is no distinguishing definition e.g., by structure to differentiate the genus claimed to any specific or genus library. Attention is drawn to applicant's newly cited Sato reference, Exhibit 1, as discussed below.

Response to Arguments

Applicants argue that the claimed subject matter does not involve the same principles in the Lilly case. The claimed

elements are not defined only by function. The structural features are either described in the specification (e.g., "identifier sequence amino acid tracts") or were available to the skilled worker at the time the application was filed (e.g., "protease sensitive sites" and individual proteins . . . being able to bind to a target of interest"). The latter two categories are well known in the art, providing the skilled worker with an instant vision of numerous species and their structures that fall within the claim scope and which distinguish them structurally from others. The identifier tracts are essentially arbitrary sequences of amino acids. Together, the skilled worker can easily envision a legion of species that fall within the claims. Unlike the Lilly case where very specific narrow structures were necessary to meet the claim requirements, the present invention involves sequences that were either known in the art or which have only minimal requirements to satisfy the claims.

In reply, the instant claim parallels the Lilly case. Like Lilly the claimed and alleged described structural feature of the generic "identifier amino acid tracts" does not define any structural features to distinguish them from others. This is made more complex when the amino acids are arbitrary sequences as stated. There is no specific

description or the requirements in the specification that categorizes a sequence as arbitrary. An arbitrary sequence would cover a huge scope of sequences. A patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion. *Brenner*, 148 USPQ at 696. The basis by which a protein is identified by these arbitrary sequences raises uncertainties. While the term proteins and protease sensitive sites are known in the art however, these two terms alone cover a huge scope i.e., not considering the arbitrarily assigned sequences. Protease sensitive sites are not descriptive of a protein. The protein cleavage site of a protein is primary sequence dependent. Without such primary sequence proteolysis can occur anywhere in the protein including the arbitrary sequence tract. This would result in a library of no use. If an applicant chooses to rely upon general knowledge in the art to render his disclosure enabling, the applicants must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288, or would reasonably be expected to check the source which applicants rely upon to complete his disclosure and would be able to locate the information with no more than reasonable intelligence. There is no

explicit description in the specification as to which proteins are protease sensitive. Claims drawn to the use of known chemical compounds must have a corresponding written description only so ***specific*** as to lead one to that class of compounds. In re Herschler (CCPA 1979) 200 USPQ 711. (Emphasis added). Applicants can rely upon prior art which would enable one skilled in the art to glean therefrom the necessary information to render the specification enabling with respect to the first paragraph of 35 USC 112 but the burden is on applicants to point out precisely where enablement lies in such disclosure. In re Albrecht II (CCPA 1975) 185 USPQ 590. Not everything, which may be cited as prior art to preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the enablement requirement of 112. Thus, there is nothing in the specification that correlates the single species to the huge scope of the different undefined structural components of the library.

Applicants argue that the sequence tracts are used to make and identify the presence of the polypeptide to which they are attached. These amino acids are arbitrary and there is no required structure recited in the claims as long as they are "unique". Applicants argue that page 4, lines 23-44, for

example, an eight-amino acid barcode sequence using 17 of the 20 natural amino acids is described. A specific example is provided at page 5, lines 1-35. Example 2, beginning on page 20, provides a specific working example of barcode sequence.

In response, while applicants might be their own lexicographer, however, the definitions of the coined term i.e., "unique" identifier tracts or barcode should be in the disclosure. The requirement that the tracts are only unique and arbitrary is not a positive description of its structure. All sequences are unique. The question is what would set apart one from the other to be included within the claimed scope. Where does the "unique" tract begins or ends in an unstructured protein?

A review of page 4, lines 23-44, provides general theory of a 13,824 tracts. It does not describe the different kind of combinations of each of the eight positions to form unique tracts for each of a billion proteins in the library.

It is not controverted that Example 2 describe a specific tract sequence and a single antibody library. However, the issue is whether this single embodiment is representative or correlate to the huge scope of the claimed library of proteins and an arbitrary unique tract. Even for this single unique sequence the specification (page 39, lines 16-24) appears to recognize some

unpredictable effects in the use of the single tract. It recites that a unique sequence barcode be designed to avoid the introduction of stop codons and further ***biased*** to exclude encoding residues with greater than two alternative codons. Thus, it is apparent that this single barcode has been specifically designed for the single library of antibody, not for any type of proteins in a library.

Applicants argue that the structural characteristics need to confer binding activity are well known in the art for binding molecules. It is not necessary to recite these specific structural characteristics where a technology is mature and well developed. Functional language suffices as stated in Enzo Biochem. Inc.

In response, applicants throughout their arguments rely on prior art knowledge but fail to produce a single prior art reciting said generic library. A method of screening a library can hardly be considered mature and well developed. The challenge still faced by skilled artisan in the art i.e., after making an enormous collection is screening said enormous library such that the desired protein is obtained. In some library some members are underrepresented and normally the desired one is not present or not properly expressed by a host cell. The Enzo case is inapplicable here, at least for the generic claims 52, 64 and

74, which do not recite antibodies. In Enzo, an antibody is not in a collection of billions of compounds as in the instant library. While antibody technology, as alleged is matured however, the library art can hardly be considered one. Applicants argue that protease sensitive sites are well known in the art and readily envision by the skilled worker. Applicants state that many protease sensitive sties are known in the prior art. Applicants cite e.g., Promega, Pierce and other sites. The exhibits clearly establish the commercial use and general acceptance of protease sensitive sites to provide a precise cleavage position to cleave off a leader amino acid sequence from a recombinant protein. The prior art cited by examiner e.g., Knappik is argued to establish that protease cleave agents were utilized successfully prior to the filing date.

In reply, as applicants recognized all proteins are protease sensitive. The question is where or which part can be cleaved when the tracts are arbitrarily designated. The specification does not describe one of the alleged commercially available proteases. The argument about these proteases is irrelevant or that the protease cleaves a leader amino acid sequence. (Is the leader sequence the same as identifier tracts)? The claimed does not recite a protease. Rather, a property of the protein. The cited prior art, Knappik in the

Background of the invention recite the numerous unpredictable factors encountered by a skilled in the art. See an illustration of this unpredictability at col. 20, lines 1-35.

Applicants argue that Factor Xa uses a protein as shown in Exhibits 2-4 as a commonly utilized in commercial protein purification. Applicants argue that the protease sensitive sites are well known in the art. It is also argued that the specification describes the structures for enterokinase, Factor Xa and thrombin cleavage sites. Applicant states that Exhibit 1 discloses other protease sites known in the art. A patent need not teach, and preferably omits, what is well known in the art.

In reply, as stated by applicant, protease acts on ***sensitive sites.*** However, it is not apparent from the claimed unstructured protein, the sites that are sensitive to an enzyme. Neither is it apparent whether the undefined site is the only site that is sensitive to an enzyme. Exhibit 1 (Eaton et al), like the specification, describes a single protein, factor VIII cleaved by thrombin, APC and Factor Xa. In the abstract at page 505, Eaton discovers that with this single protein one of the enzymes activates and inactivates factor VIII. At page 506, Eaton states, "…other than species differences, the reasons for this discrepancy is (are) unknown……." Further, at page 507,

col. 2, first incomplete paragraph, Eaton states "…..the site at which this cleavage occurs has yet to be determined…"

Clearly the art, at the time of applicant's invention, like the specification describes studies for single or specific protein having definite structure. Even with the single protein having a defined structure, Eaton indicates the uncertainty in the art i.e., discrepancies of results obtained from one enzyme to another. What more for a collection of millions of unstructured proteins, as claimed? A true test of any prior art relied on to show or suggests that a chemical compound is old i.e., known in the art, is whether the prior art is such as to place the disclosed "compound" in the possession of the public. If merely listing compounds could suffice as a disclosure, it would bar patent protection to the person who actually discovered a compound on the list and, in so doing, thwart the Constitutional purpose of the patent system. See in re Wiggins, 488 F.2d 538, 179 USPQ 412(CCPA 1973). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. In biotechnological invention one cannot necessarily claim a genus after only describing a single species because there may be unpredictability in the results obtained from

species other than those specifically described. Refer again to the Sato reference.

Applicant states that Capon et al v. Eshhar et al v. Dudas is not restricted only to antibodies but to other additional elements such as transmembrane and cytoplasmic and extracellular domain. None of these recites specific structural features. The court did not find the claim invalid and concluded that the precedent did not establish a per se rule.

In response, the claim to a single protein, antibodies and its additional elements are still a single protein even in the presence of the auxiliary elements. The instant library of no defined structure is not a single protein. Rather a collection of enormous proteins also containing auxiliary elements as the tracts.

The fact situation in the Capon case is not similar to the instant case. The claimed invention claims a library (mixtures) of numerous combinations of different proteins including but not limited to antibodies, antigens (e.g., viral, bacterial, tumor and etc.), enzymes, growth factors and other unnamed or unstructured proteins. Considering that this is but one of the many undefined structures of the genus claim. Thus, the infinite undefined variables of the claimed protein library cannot be

completely described by the single protein species, scFv antibody in the specification.

C). ***Scope (Enablement) Rejection:***

Claims 52-74, as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for scFv with specific barcodes and enzyme, does not reasonably provide enablement for any type of proteins, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims and repeated below.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the scope (enablement) requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the kind, number

and length of tract of amino acid within any type of protein that can be cleaved by an enzyme, the type of enzyme that cleaves a protein, the kind of proteins (or tracts) that retains its capability of binding to a target when proteolyzed.

2). The specification failed to provide working examples for the broad scope of the claimed library and method. Example 2 of the working example describes only a scFv with a random tract cleave by a V8 protease.

3). The breadth of the claims encompasses a large diversity of protein library with an amino acid sequence tracts, proteases and the predetermined sites of variations in the amino acid tract. It is well known in the art, that it is often difficult to know where a protease cleaves a protein. Too often an enzyme cleaves a protein at a different site, rather than at the intended site, resulting in an inactive cleaved protein. See Sato above.

4). The state of the prior art is such that techniques are applied specifically for a predetermined protein with specific mutations thereof, if any, and target protein.

5). The art is inherently unpredictable because it is not possible to predict which predetermined amino acid tract would be cleaved by an enzyme having the ability to bind to its target. It is generally known that the conformational freedom

that promotes binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and which sites in a particular protein are best suited to insertion of multiple independent sequences. The complex spatial configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds).

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous amino acid tract in a protein would result in a protein library that binds to a target of interest without undue experimentation. Applicants do not adequately

enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

The language of the claim is so broad that it causes claim to have a potential scope of protection beyond that which is justified by the disclosure.

Response to Arguments

Applicants argue that given the mature state of the art and availability of the recited elements in the claims, render the claims enabling as to the methods of producing identifier tracts. The use of protease sensitive sites in fusion proteins is known and predictable and the binding proteins are also known, including the sequences.

In response, the different factors recited above and applicants' stipulation in the specification for a single tract used for a single protein, antibody, can hardly be considered predictable of a species for the genus as broadly claimed.

Claim Rejections - 35 USC § 102

Claims 52-57, 61, 64-70 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Matthews et al (Science) and repeated below.

Matthews discloses at e.g. page 1113 up to page 1116, specifically Fig. 1 a library of proteins with a library of random peptide, Table 1 inserted between the protein hGH and phage. At page 1114 a method for identifying protease substrates from a library of possible peptide sequences is described. The method involves constructing a library of fusion proteins containing an amino terminal domain used to bind to an affinity support followed by a randomized protease substrate sequences and the carboxyl terminal domain of M13 gene 111.Each substrate sequence is displayed on phagemid particles between a human growth hormone that binds to the hGH-binding protein and a truncated form of the gene III protein. The phage library is disclosed at page 114, col. 2 and Factor Xa. Accordingly, the library and method of Matthews that recites specific protein with the specific library fully meet the broad claimed library and method using a library of no defined structure/sequence.

Response to Arguments

Applicants argue that in Matthews there is no individual identifier sequence amino acid tracts which are unique to said individual proteins.

In reply, attention is drawn at page 1114, col. 2, 2nd paragraph of Matthew which recites a phage library wherein the sequence GPGG(X)5GGPG is inserted in the phage library. The

inserted sequence is encompassed by the broad undefined claimed and applicants' coined term "identifier tracts".

Claim Rejections - 35 USC § 103

Claims 52-70 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knappik (USP 6300064) in view of either Ring (USP 5,849,877) or Markland et al (WO 92/15679) as reiterated below.

Knappik discloses e.g., abstract, a library of antibody (protein, as claimed) with synthetic consensus sequences (individual amino acid sequence tracts) having protease cleavage sites. Knappik discloses at col. 7, line 60 up to col. 13, line 3 that the complete collection of (poly)peptide sequences represent the complete structural repertoire of the collection of homologous proteins. These artificial (poly)peptide sequences are then analyzed, if possible, according to their structural properties to identify unfavorable interactions between amino acids within said (poly)peptide sequences or between said or other (poly)peptide sequences, for example, in multimeric proteins. Such interactions are then removed by changing the consensus sequence accordingly. The (poly)peptide sequences are then analyzed to identify sub-elements such as domains, loops, helices or CDRs. The amino acid sequence is back translated into a corresponding coding nucleic acid sequence which is adapted to

the codon usage of the host planned for expressing said nucleic acid sequences. A set of cleavage sites is set up in a way that each of the sub-sequences encoding the sub-elements identified as described above is flanked by two sites which do not occur a second time within the nucleic acid sequence. This can be achieved by either identifying a cleavage site already flanking a sub-sequence of by changing one or more nucleotides to create the cleavage site, and by removing that site from the remaining part of the gene. The cleavage sites should be common to all corresponding sub-elements or sub-sequences, thus creating a fully modular arrangement of the sub-sequences in the nucleic acid sequence and of the sub-elements in the corresponding (poly)peptide. Knappik further discloses sets up two or more sets of (poly)peptides (i.e., library), where the cleavage sites are not only unique within each set but also between any two sets. The libraries comprises for example, but not limited to, two domains from antibodies such as VH or VL or two extracellular loops of transmembrane receptors. Moreover, Knappik discloses libraries of antibodies or antibody fragments, preferably single-chain Fv, or Fab fragments, which may be used as sources of specificities against new target antigens. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps

of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule is also disclosed. An scFv fragment library comprising the combination of HuCAL VH3 and HuCAL V.kappa.2 consensus genes and at least a random sub-sequence encoding the heavy chain CDR3 sub-element is screened for binding antibodies. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated. Knappik also discloses a method in which one or more of the genetic subunits (e.g. the CDRs) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are selected, collected and used as starting material for the next library. One or more of the remaining genetic subunits are randomized as described above. See further the EXAMPLES at col. 15, line 50 up to col. 28, line

60. Knappik further discloses at col. fusion proteins by providing for a DNA sequence which encodes both the (poly)peptide, as described above, as well as an additional moiety. The additional moiety may confer on its (poly)peptide partner a means of detection and/or purification. For example, the fusion protein could comprise the modified antibody fragment the additional moieties such as the commonly used C-myc and FLAG tags (Hopp et al., 1988; Knappik & Pluckthun, 1994).

Knappik fails to disclose that the endoprotease is Factor Xa as in claim 57. However, Ring discloses at col. 34, line 65 up to col. 35, line 25 the proteolytic cleavage of an isolated sFv from its leader sequence fusions to yield free sFvs, which can be renatured to obtain an intact biosynthetic, hybrid antigen-binding site. The cleavage site preferably is immediately adjacent to the sFv polypeptide and includes one amino acid or a sequence of amino acids exclusive of any one amino acid or amino acid sequence found in the amino acid structure of the single polypeptide chain. The cleavage site preferably is designed for specific cleavage by a selected agent. Endopeptidases are preferred. Many useful cleavage agents, for instance, blood coagulation Factor Xa and enterokinase recognize and preferentially or exclusively cleave at particular cleavage sites. Useful enzymes recognize multiple

residues as a cleavage site, e.g., factor Xa (which recognizes a four amino acid sequence of Ile, Glu, Gly and Arg residues, respectively), or enterokinase (which recognizes a five amino acid sequence having four Asp residues, and one Lys residue, respectively). Markland discloses at page 21, lines 5-20 that display peptides having high affinity for the target may be quite difficult to elute from the target, particularly a multivalent target. One can introduce a cleavage site for a specific protease, such as Factor Xa, into the fusion protein so that the binding domain can be cleaved from the genetic package. Such cleavage has the advantage that all resulting phage have identical coat proteins and therefore are equally infective. The step allows recovery of valuable gene which might otherwise be lost. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use protease digestion in the library of Knappik, specifically Factor Xa for the advantage provided by e.g., Markland above. Such advantage would motivate one having skill in the art since this advantage provides for the recovery of valuable genes which might otherwise be lost if protease cleavage is not used.

Claims 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knappik in view of Markland or Ring as

applied to claims 52-70 and 73-74 above, and further in view of Hutchens (USP 6734022).

Knappik is discussed above. Knappik does not disclose mass spectrometry i.e., MALDI-Tof determination of the peptide sequence. Hutchens discloses at col. 5, line 35 up to col. 6, line 60 a method for desorption and ionization of analytes in which unused portion of the analytes contained on the presenting surface remain chemically accessible, so that a series of chemical and/or enzymatic or other treatments (e.g., discovery of analyte-associated molecules by molecular recognition) of the analyte may be conducted on the probe tip or other presenting surface, in situ, followed by sequential analyses of the modified analyte by mass spectrometry. In one case (i.e., repetitive sequential analyses) the analyte is adsorbed to the sample presenting surface and can be treated (modified in situ after the excess free matrix is removed (i.e., washed away). Matrix can be added back before analysis by mass spectrometry. Using this procedure, an analyte can be repeatedly tested for a variety of components by removing one matrix, modifying the analyte sample, re-applying the same or different matrix, analyzing the sample, etc. or groups of biological or other macromolecules under investigation, or subsequent examination (e.g., quantification and/or structure elucidation) by mass

spectrometry. This has the advantage of achieving both the purification of the analyte sample previously required and the effect of concentrating the analyte. It reduces by a factor of 1,000 to 100,000 the amount of analyte needed for the mass spectrometry examination, since only the macromolecules which attach to the biospecific affinity reagents are removed from the analyte sample, and these can be sequestered on predetermined areas of the probe tips or sample plates that are even less than the laser spot size.

It would have been obvious to one having ordinary skill in the art to use MALDI-Tof in the method of Knappik for the advantage taught by Hutchens. The advantage, supra, would motivate one having ordinary skill in the art.

Response to Arguments

Applicants acknowledge that Knappik describes a library of modular DNA sequences that code for antibodies, which contain nucleotide cleavage sites that separate sub-sequences in the DNA. The subsequences correspond to different protein coding domains. But argue that these are not proteinase sites. The DNA cleavage sites are utilized to selectively modify domains within the coding DNA sequence. It is further recognized that Knappik suggest additional moieties including FLAG tags. The FLAG tag arrangement, as explained in Hopp et al., includes a "marker

segment" ('FLAG tag) and a protease cleavage site, e.g., enterokinase. See, e.g., Hopp et al., Page 1205. The marker sequence can be used for purification purposes, e.g., by providing a binding site for an antibody. However, a FLAG tag and an accompanying cleavage site, does not disclose or suggest the claimed arrangement, e.g., proteins comprising ... one or more individual identifier sequence amino acid tracts which are unique to said individual protein when bound to the specific target of interest, and are flanked by one or more protease sensitive sites. Compare pending Claim 52. The FLAG tag is not described as unique to the individual proteins, but is the same for each one. No motivation with an expectation of success has been provide in the rejection for modifying Knappik et al. to have arrived at the present invention. It is further argued that none of the cited references, Ring et al, Markland and Hutchens describe one or more individual identifier sequence amino acid tracts, which are unique to, said individual protein when bound to the specific target of interest. Compare Claim 52.

In reply, attention is drawn to col. 8, lines 20-47 and col. 14, lines 11-40 which discloses the use of unique tracts and cleavage sites. The disclosure about Hopp et al recites only the enzymatic cleavage using enterokinase and not to the use of FLAG as the unique sequences. Knappik discloses at col. 14 also

the translation of the DNA to its corresponding polypeptide. It would be within the ordinary skill in the art to use the corresponding protease since Knappik discloses the DNA encoding protein. As stated by applicant above the protease sensitive sites is well known in the art. The prior art cited by applicant, inter alia, Hopp, also cited by Knappik, discloses other protease sites known in the art. The cited references, Ring et al, Markland and Hutchens are employed not for the purposes as argued, since Knappik teaches said identifier tracts. Rather, these references are employed in combination with Knappik for the reasons why one having ordinary skill in the art would be motivated to use the specific component, e.g., Factors Xa or the MALDI-Tof means of detection. One cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). The test for obviousness under 35 USC 103 is not the express suggestion of the claimed invention in any or all of the references but what the references taken collectively would suggest; and inferences which one skilled it in the art would reasonably be expected to drawn from the disclosure in the references. In re Preda, 159 USPQ 342 and In re Conrad, 169 UASPQ 170.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 16-51 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner

Art Unit 1639

Tdw

May 11, 2006